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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/732,862	12/10/2003	Katelynne Lyons	LOR-136.0 (9720/88881)	9117

24628 7590 03/03/2009

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EXAMINER	
PENG, BO	
ART UNIT	**PAPER NUMBER**
1648	

MAIL DATE	DELIVERY MODE
03/03/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/732,862	LYONS ET AL.	
	Examiner	Art Unit	
	BO PENG	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 January 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-47* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-47* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on January 20, 2009, has been entered.

2. Claims 1-47 are pending and considered in this Office action.

Claim Rejections – 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. **(New rejection)** Claims 1-47 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The following quotation from section 2163 of the Manual of Patent Examination Procedure is a brief discussion of what is required in a specification to satisfy the 35 U.S.C. 112 written description requirement for a generic claim covering several distinct inventions:

> The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice..., reduction to drawings..., or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus... See Eli Lilly, 119 F.3d at 1568, 43 USPQ2d at 1406.
>
> A "representative number of species" means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus.

It is also noted that even the presence of multiple species within a claimed genus does not necessarily demonstrate possession of the genus. See, In re Smyth, 178 U.S.P.Q. 279 at 284-85 (CCPA 1973) (stating "where **there is unpredictability in performance of certain species or subcombinations other than those specifically enumerated**, one skilled in the art may be found not to have been placed in possession of a genus or combination claimed at a later date in the prosecution of a patent application."); and University of California v. Eli Lilly and Co., 43 USPQ2d 1398, at 1405 (Fed Cir 1997)(citing Smyth for support). Thus, when a claim covers a genus of inventions, the specification must provide sufficient written description support for the entire scope of the genus. Support for a genus is generally found where the applicant has provided a sufficient number of examples so that one skilled in the art would recognize from the specification the scope of what is being claimed, or provided a function and a structure correlating with that function. Moreover, in situations where the operability of species other than those provided is uncertain, additional support is required over that which would be required where greater certainty is present.

5. The scope of the claims encompasses a large number of HBc chimers that contain a 5% substitution frequency in SEQ ID No: 1 (183 amino acids). The claims further require that the specified HBc particle has enhanced stability comparing to wt HBc. In support of the claims, the specification shows a few species of HBc chimer (for example, 7 of 24 chimers in Example 14) were able to yield particles, see Table 13, Example 14. Of the modified HBc chimers in the above example, however, 14 of the 24 tested lost their ability to form particles. Thus, the specification shows that it is uncertain if HBc chimers containing a 5% substitution frequency in SEQ ID No: 1 can form viral-like particles as can HBc, or would the resultant HBc particles have enhanced stability as claimed.

6. As discussed in the previous Office actions, the art indicates that the result of peptide modification is, in general, unpredictable. Modification of a peptide by as little as one amino acid can cause a change in conformation, and thus peptide function, that can't be predicted in advance. See Rudinger, J. at page 6 (Cited in the previous Office action). Metzger teaches that a single amino acid change, Pro-138 to Gly, prevents self-assembly of the HBc protein into particles (Metzger, J. Gen. Virology, 79:587-590, 1998). Thus, substitution of a single amino acid can result in an unpredictable effect on the assembly of HBc particles. These teachings in the art are consistent with the result shown in the specification Example 14.

7. Although the specification discloses a few species of modified HBc chimers, the specification has also illustrated that most amino acid changes in HBc result in an inability to form particles. The specification has failed to provide an adequate description which amino acid substitution in the HBc chimers can still form viral-like particles, and

has enhanced stability comparing to wt HBc. Given that the scope of the claims encompasses a large number of modified HBc chimers, and considering the unpredictable stability of the majority of modified HBC chimers, the specification has not disclosed sufficient species of modified HBc chimers that have enhanced stability to support the broadly claimed genus. Consequently, the skilled artisan would reasonably conclude Applicant was not in possession of the claimed HBc chimers containing a 5% substitution frequency of amino acid residues in the HBc SEQ ID NO: 1 resulting in enhanced stability.

8. **(Prior rejection-maintained)** The rejection of Claims 1-47 under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement (scope of enablement), **is maintained** for the reason of record.

In response to Applicant's argument:

9. Applicant argues that the specification enables the scope of the claims because specification [0231]-[0234] teaches use of LASERGENE software to assist in determining which amino acid residues can be changed without a loss of biological activity or the ability to form particles.

10. This argument is not convincing. While a computer program may help one of ordinary skill in the art to chose which amino acids could be altered, such general direction is not sufficient to predict if the proposed changes would actually result in a desired property, such as enhanced stability, of the modified HBc. It is noted that, even with the assistance of LASERGENE software, the specification has shown that modified HBc chimers containing changes of two or three amino acids (less than 5% substitution

of amino acid residues in the HBc SEQ ID NO: 1), totally abolish their ability to form particles, See example 14 and table 13. Thus, the specification apparently does not support applicants' argument. The rejection is maintained.

Claim Rejections - 35 USC § 103

11. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

12. **(Prior rejection-maintained)** The rejection of Claims 1-6, 8-14, 16-28, 30-42 and 46 under 35 U.S.C. 103(a), as being unpatentable over Pumpens, in view of Zlotnick and Zhang, **is maintained** for the reasons of record.

13. Applicant argues that the Zlotnick manuscript is not supportive of the premise that *C*-terminal cysteines enhance stability because the publication's experimental design lacks proper controls and therefore conclusions gleaned from it are suspect.

14. This argument is not convincing. The Zlotnick manuscript is published in a peer-reviewed scientific journal. This indicates that one of ordinary skill in the art and one who has been judged to be critical of experimental design quality has accepted the evidence and conclusions presented in the Zlotnick manuscript. It is noted that the instant specification also recites the Zlotnick manuscript as analogous art, see Para [0009]. Thus, Applicant's argument is not convincing.

15. Applicant again argues that the combination of Zlotnick, Zheng and Pumpens does not teach that the modification of positions 48 and 107 of HBc and the addition of a cysteine residue at the *C*-terminus would increase stability.

16. This argument has been found not persuasive in the previous Office actions dated November 17, 2006, May 15, 2007, and July 22, 2008. The rejection is maintained for the same reasons of record.

17. **(Prior rejection-maintained)** The rejection of Claims 1-6, 8-28, and 30-46 under 35 U.S.C. 103(a), as being unpatentable over Page and Birkett, both in view of Zhang, **is maintained** for the reasons of record.

In response to Applicant's argument:

18. Applicant presented the argument that the combination of Page, Birkett and Zhang does not teach the claimed HBc chimer based on targeting of the references individually. Specifically, Applicant argues: "it must be noted that Page describes hybrid HBc capsid molecules having the three or four arginine repeats at the *C*-terminus deleted. The molecules of the present invention do not have the arginine repeats removed. As such, whatever Page may teach is not relevant to the present molecules as they are significantly different" (Remarks, Para 4, p. 26). Applicant further states: "It should be noted that the molecules of the present invention, **besides retaining the arginine repeats** also have the cysteines removed at positions 48 and 107" (Remarks, Par 3, p. 27).

19. The above argument is not convincing. First, this argument is inconsistent with the claims. In contrast to Applicant's assertion that"... the molecules of the present

invention, **besides retaining the arginine repeats**, ..." Claims 25-46 require domain IV of the chimer "contains fewer than about ten arginine or lysine residues or mixture of both residues..". It is noted that Page teaches that HBc contains 4 arginine repeats, which have 17 arginine residues, from amino acids 150 to the *C*-terminus of HBc, See Fig. 1. Page teaches hybrid HBc capsid molecules having the three arginine repeats at the *C*-terminus deleted, wherein three arginine residues are retained, see e.g. Fig. 1. Thus, this hybrid HBc capsid molecule appears to meet the structure element described in Claim 25 (independent claim) domain IV. Page teaches "[t]he removal of the arginine repeats residues the binding of nucleic acid, whilst retention of the *C*-terminal cysteine allows for the formation of a disulphide bond which in the native structure is important for the formation of a stable particle." (See page 2).

20. Secondly, as indicated in the previous Office actions, Zhang shows that HBc mutants that lack Cys at either position 48 or 107 yield stable dimers, without detectable monomers (See Figure 3, lanes 3 and 7). In view of the combined teaching of Page and Zheng, one of ordinary skill in the art would apply such knowledge to make a chimer HBc without Cys 48 and 107, while retaining the *C*-terminal cysteines, in order to achieve more stable HBc particles. Therefore, the invention as a whole is obvious to one of ordinary skill in the art, in view of the prior art. The rejection is maintained.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not

identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

21. **(Prior rejection-maintained-extended)** The rejection of Claims 1-46 under the judicially created doctrine of obviousness-type double patenting, as being unpatentable over (1) Claims 1-78 of 09/930,915 ('915); (2) Claims 1-53 of 10/787,734 ('734); (3) Claims 98-109 of 10/805,913 ('913); (4) Claims 79-115 of 10/806,006 ('006), (5) Claims 47-85 of 11/508,655 ('655), **is maintained**. Claims 1-46 are also rejected under the judicially created doctrine of obviousness-type double patenting, as being unpatentable over (6) Claims 1-22, 25 and 26 of new application 11/507,083 for the same reason as that for co-pending applications '915, '734, '913, '006 and '655 above.

22. **(New rejection)** Claims 1-6, 8-28, and 30-46 are rejected on the grounds of nonstatutory obviousness-type double patenting as being unpatentable over Claims 1-19 of U.S. Patent No. 6,231,864 ('864), in view of Page, *et al* (WO 01/98333 A2, cited in the previous Office action) and Zheng (1992, J. Biological Chemistry, Vol. 267 (13): pp.

9922-9429, cited in previous Office action).

23. Claims 1-9 of '864 teach a modified hepatitis B core protein comprising a chemically reactive amino acid residue, preferably in an immunodominant region of the nucleocapsid protein. The modified hepatitis B core protein or its aggregated nucleocapsid protein particles can be pendently linked to a hapten to form a modified nucleocapsid conjugate. The modified hepatitis B core protein can also be modified to include a T cell epitope.

24. Page teaches the use of HBcΔ as a vehicle for the presentation of epitopes. Page teaches a modified HBcΔ chimer where one or more of the four arginine repeats responsible for RNA binding at the *C*-terminus (between 150-180) have been deleted followed by the addition/retention of a *C*-terminal cysteine residue.

25. Zheng teaches the function of native cysteines in formation of HBc particles. Zheng teaches that the intra-chain disulfide bonds are not essential for core particle formation, but inter-chain disulfide bonds are involved in formation of HBc capsid dimers with the identical residues of another monomer. Zheng also teaches that the native Cys107 is buried within the particle structure and is not involved in HBc capsid formation. The native Cys61 and Cys183 are always, and Cys48 is partially, involved in inter-chain disulfide bonds with the identical residues of another monomer.

26. One of ordinary skill in the art would have been motivated to combine the teachings of Birkett with that of Page and Zheng in order to make an HBcΔ molecule that could present an epitope *via* a side-chain. One would have been motivated to do so, and would have had a reasonable expectation of success, given the knowledge that both HBc and HBcΔ have been successfully used for displaying heterologous epitopes on HBc

particles, as taught by Birkett and Page, and given the knowledge that methods for operatively linking individual haptens to polypeptides through an amino acid residue side chain to form an immunogenic conjugate are well known in the art, as taught by Birkett, see e.g. col. 13 and 14, and also given the knowledge that native Cys48 and Cys107 are not essential for HBc dimer formation, as taught by Zheng. Therefore, the instant claims would have been *prima facie* obvious over Claims 1-19 of U.S. Patent No. 6,231,864 ('864), in view of Page and Zheng.

Remarks

27. No claim is allowed.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bo Peng, Ph.D. whose telephone number is 571-272-5542. The examiner can normally be reached on M-F, 9-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce Campell, Ph. D. can be reached on 571-272-0974. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

/Bo Peng/
Patent Examiner, AU1648